PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-317WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/05945	International filing date *(day/month/year)* 15.12.2003	Priority date *(day/month/year)* 16.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D498/06		
Applicant RANBAXY LABORATORIES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.07.2004	24.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Frelon, D Telephone No. +49 30 25901-312

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/05945

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-7 as originally filed

Claims, Numbers

1-25 as originally filed

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 18-25 regarding the industrial applicability

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 18-25 regarding the industrial applicability

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claims 18 and 25 are directed to methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods. They relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT.

No opinion is formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34 (4) (a)(i) PCT). For the assessment of the present claims 18 and 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Novelty

1.1 Process claims 1-17

The presently claimed process is essentially characterised by the control of the "moisture content of the reaction mass" which is to be between 0.5%w/w and 1.5%w/w followed by the isolation of the "pure" levoflaxine hemihydrate (***Note: the characteristic which presently appears to be an essential feature of the invention cannot be let blurred by the term "about". "About" is therefore considered as null and void***).

The "moisture content of the reaction mass" is not clearly defined in the application. This vague expression necessarily also encompasses the water content described in the prior art D1 which, consequently, in the absence of more specificity, appears novelty destroying. D1 describes also the preparation of levofloxacine hemihydrate by means of controlling the water content during crystallisation. The water content is said to be low (claim 2) to produce the hemihydrate in order to prevent the monohydrate formation and, more specifically, ranges from "about" 2 to "about" 10% (claims 7 and 27).

Considering the examples of preparation of the hemihydrate: in example 1 of D1, a moisture content of 2.50% is given by the Karl-Fischer's method; the Karl-Fischer's method gives a moisture content of 2.4% in the unique example of the present application. It is noted that, in the absence of a clear definition of the "reaction mass" and considering the unique example as a legitimate illustration of the present invention, the moisture content of 2.4% given in this example should have its correspondance in the range of 0.5%w/w to 1.5%w/w claimed for the "moisture content of the reaction mass".

D2 discloses also for the preparation of the hemihydrate with a water content found at 2.40% (table 1).

D1 and D2 are therefore novelty destroying against process claims.

The presently claimed process must be unambiguously distinguishable from the prior art by one (or more) clearly identifiable feature(s) which is (are) still to be defined.

1.2 Compound claims 19-23

1.2.1 The levofloxacin hemihydrate is known. The fact that a higher degree of purity can be obtained by a (novel) process does not confer novelty to the compound which is already structurally well defined. On page 6 of the description, the "pure" levoflaxine hemihydrate is defined as having a purity of more than 99%. D4 claims purities of 99% and greater for the levoflaxine hemihydrate prepared according to its process (see examples and claims). "Pure" levoflaxine hemihydrate of claims 19 to 22 is therefore not novel.

1.2.2 The powder method of X-ray diffraction of figure 1 gives one peak at 6.680° and

one peak at 13.100° in the present application. In example 1 of D1, two peaks are said to be characteristic at 6.7° and 13.2°. Under the reservation that the mesuring methods (instruments) are quite comparable, these data appear very similar on both sides.
D2 gives analogous data: characteristic diffraction peaks at 2theta = 6.5, 12.9°.

On page 6 of the description, the "pure" levoflaxine hemihydrate is also defined as being obtained "essentially free of monohydrate", *i.e.* wherein the monohydrate is not detectable by X-ray diffraction technique, given a threshold of 0.25%. An appropriate specification with X-ray diffraction characteristics which were not disclosed in the prior art could restore the novelty of corresponding claims.

If the Applicant is willing to claim a novel crystalline form, the characterisation of this crystal (its technical features) must be accurately set: with X-ray diffraction pattern data, the relevant conditions for obtaining these data (apparatus, physico-chemical requirements, etc) should be also given. It is noted that D1, D2 and D3 provide X-ray data. It should have been evidenced that these data differ significantly from the ones given in the present application.

1.3 Pharmaceutical composition of claim 24

For the same reason, the pharmaceutical composition of claim 24 is not novel as presently claimed. The purity of the known product does not render its pharmaceutical application novel.

2. Inventive step

2.1 According to the description, the problem is to provide a process to prepare pure levofloxacin hemihydrate.

2.2 Due to the lack of novelty, essentially because of the unspecific terms "about", "reaction mass" and "pure", the inventive step cannot be substantially examined. If the claimed subject-matter could have been made novel by means of clear and essential differentiating features, it should also have been demonstrated that these specific

characteristic(s) are responsible for a unexpected technical effect as, for instance, a surprising improvement in the purity of the product.

2.3 The prior art, especially D1 (page 3) and D2 (abstract), teaches clearly that the obtention of highly purified and stable levofloxacin hemihydrate is linked to the moisture control of the reaction medium. D1 specifies the need for a control of the water content of the aqueous solvent and D2 analyses the dehydration effect on the formation of levofloxacin hemihydrate (among other forms of levofloxacin). The prior art also teaches the close dependency on the temperature.

Note that the "pure" commercial argument put forward on page 2 is irrelevant to assess the inventive step when no technical effect originates such an advantage.

In addition to a specific moisture content, temperature and solvent may also appear essential to an inventive process.